

Unit 2-4, Rolling Hills Condo
Lenox, MA 01240
20 November 1993

President Torsten Wiesel
The Rockefeller University
New York, NY 10021

Dear Doctor Wiesel:

This letter is to offer a comment and suggestion concerning the current and forthcoming celebration of the 50-year anniversary of the Avery, MacLeod and McCarty discovery. I am addressing this from the standpoint of a participant of the DNA work which immediately followed that great accomplishment.

First, however, I must offer my late thank-you for all that you have been doing for The Rockefeller University--to which my attachment is still deep after my 47 years there. Becoming Emeritus in 1982, and retiring to SUNY, Albany as adjunct faculty, just before you came to our campus, I've not found the opportunity to meet you during these last eventful years. I did anticipate your generous stimulus to Rockefeller University, though, remembering the wonderful spirit you and Dr. Hubel manifested before many of us at Columbia's Louisa Gross Horwitz dinner in 1978; I was among the many who greeted you there then.

Returning to present concerns: my feeling is that The University loses some of the credit--and publicity--it deserves about the Avery-McCarty DNA finding. The simple fact is that several of the next developments extending and interpreting the meaning of it occurred almost uninterruptedly right on its campus. Please permit me to sketch, as briefly and impersonally as I can manage, what I see as the history of that discovery during the next ten years--leading substantially and fairly directly--I would maintain--to the works of Alfred Hershey and of James Watson and Crick that are of course quite well known....

At Rockefeller, Maclyn McCarty about 1946 moved into streptococcal disease work, in which I know he explicitly hoped and intended to apply a knowledge of his pneumococcal transformation work--though it turned out differently. But Mac continued to write or lecture from time to time, expressing his understanding of bacterial genetics.

That allowed me, in 1946, to join Dr. Avery in his last two years pre-retirement, and I began a concentration on bacterial transformation which continued for about thirty years. One first year Dr. Harriett Taylor continued her work there too, then I was essentially alone until about 1952, when increasing interest brought a series of postdoctoral and student collaborators. Thus the Rockefeller Institute gave continuous support, and can, I think, be pleased that the subject never left its original home.

Now, a short digest of that topic as it developed for ten years: Certainly, the Avery et al work was "complete" in supporting its own claims. Yet it provoked somewhat puzzled interest among biochemists and geneticists (interest to a scientist, of course means something like "worry" and "anxiety") as to its generality and eventual meanings. Two broad questions preoccupied them: was it actually DNA, and only DNA, which changed bacteria?--and, what do the changes in bacteria have to do with genetics, in particular, the genetics of other than cell surface traits, and the genetics of other than bacteria? Much history has been written by people too young to have known well the concerns of that next decade,

but my notes, records and publications satisfy me that I was moving pretty directly to satisfy these broad and unifying questions.

By 1954 my Rockefeller research had shown that the DNA could be quantitatively freed of protein and yet remain active, and that it was chemically very similar to classical calf thymus DNA and yet different from it in detail. DNA was shown to behave as a classical array of bacterial genes, including those for traits other than surface antigens, especially for newly derived specific mutations, and were demonstrated to convey certain pairs of linked genes. Quantitation of cell-with-DNA interaction was initiated, and study of the mechanism was begun.

These facts are accessible for your possible purview, in a short, separate listing; also enclosed is a 1979 NY Academy paper documenting my experiences and others' responses to the Avery work then and later.

Some related work was going on during that decade from other laboratories--most of it done by workers formerly associated with Dr. Avery: Colin MacLeod, Harriett (Taylor) Ephrussi--with some associates. I think it is fair to say that most of the approach to the broad questions I mentioned was still centered at Rockefeller during the decade preceding Watson and Crick. By 1954 only one other species--Hemophilus influenzae, had been transformed (Hattie Alexander's group, at Columbia), essentially reproducing the Avery findings, and some of our later ones. Later of course, other species including Bacillus subtilis and eventually E. coli became important subjects for DNA transformation--presumably helped by all of these first studies.

What can this mean for present policy? It doesn't alter our anniversary celebration of the 1943-44 events, of course. But I believe that the University, in its administrative and public relations offices ought to be conscious of a pride not only in the 1944 discovery of DNA activity, but also in their uninterrupted support of the next steps of integration of that discovery into the fabric of classical genetics. At some points now and then, such a consciousness might affect the more public policies or statements emanating from it. My remarks naturally can be considered self-serving as well as reporting University history, but I intend to keep them within the walls of our institution.

This letter was prepared before I came to New York City for Thanksgiving week, but a phone call showed me that you would not be available then. I hope we can meet another time. May I have now, your approval for me to share the essence of this letter also with Drs. Maclyn McCarty, Alec Bearn, and Norton Zinder?

I'll also be asking your secretary how to get some University mailings that I now don't. I was a bit distressed to receive notice of the 50-year celebration of the Avery 1944 paper in a multigraphed form letter addressed as "Friend of the University". Luckily, Norton Zinder also wrote me about possible round-table participation next year. (Last year, I unfortunately received no word nor notice of the opening of the new Rockefeller Research Building, and missed the occasion. Since then, Merrill Chase has seen to it that I receive the News & Notes--still somewhat irregularly.)

Sincerely yours

Rollin D. Hotchkiss
ROLLIN D. HOTCHKISS

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SUMMARY OF THE CONTINUATION AT ROCKEFELLER INSTITUTE DURING 1946-1954 OF
DNA TRANSFORMATION WORK, FOLLOWING AVERY and McCARTY (Rollin D. Hotchkiss)-

Briefly, my Rockefeller research showed or indicated the following broadening and generalizing of the chemical and genetic implications:

1. Quantitative studies showed: DNA containing absolutely no analytically detectible protein was still active; crystalline DNase, like McCarty's purified enzyme specifically inactivated transformation. These things were essentially, quantitative confirmation of McCarty's qualitative findings.
2. The transforming system was considerably simplified and made more efficient and reproducible in vitro.
3. Developing independently the first chromatography of nucleic acid bases, I showed the DNA had the expected four bases, but no uracil (or RNA); I had begun to show differences between different DNA's--though Erwin Chargaff and coworkers soon overtook any progress I could make on my own. (In the process, I discovered the first "exceptional" DNA base, 5-methyl-cytosine, in thymus DNA.)
4. By 1951 I could report transformation of several pneumococcal drug-resistance traits, and use these to isolate and quantitate the actual transformed cells, measuring time and concentration kinetics, and optimization. This surely helped others to begin DNA transformation in other bacterial and cell species, which hardly began until 1956-58 (with one exception; see below).
5. The connection of transformation to genetics was shown; stepwise drug-resistance mutations were reproduced (transferred) in identical steps of transformation induced by the DNA from the mutated bacteria.
6. Independent mutant properties were shown to be transferred independently (DNA segmented) into separate recipient cells---however:
7. By 1954 we showed (with the help of Julius Marmur) that two biochemically independent traits were transferred together into transformed pneumococci exhibiting all the characteristics of classical genetic linkage. This supported directly the idea that genes were joined to genes by more DNA--in long chains, not as "beads" interrupted by protein linkers.
8. The work with Marmur also showed that an enzyme we could identify as mannitol phosphate dehydrogenase, was controlled by a DNA gene which was transferrable irrespective of its induced or non-induced state.

Other results showing up during that decade from other laboratories were mostly those of workers formerly associated with Dr. Avery: Colin MacLeod, Harriett (Taylor) Ephrussi--with some associates--or, in one case, by Dr. Hattie Alexander, at Columbia Medical School, who with associates Leidy, Zamenhof and Redman, essentially reproduced several of the Avery, and our later, pneumococcal findings in Hemophilus influenzae. Of these, I feel that only some of Harriett Ephrussi's work at Paris during that decade bore upon the general questions mentioned above as centering at Rockefeller.

[Subsequent to 1954, those mentioned continued, and more laboratories joined and expanded the lines of DNA investigation to other bacterial species, viruses, and finally to animal and plant cells. At Rockefeller, those taking part in the next decade in related work include Norton Zinder, Alexander Tomasz, Roger Herriott and Joshua Lederberg (when he was at Stanford University).]